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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,273	07/31/2007	Jakov Vaisman	64734(70403)	6986

21874 7590 04/29/2008

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
04/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,273	VAISMAN, JAKOV	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet , 10 January 2006* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63- 75 and 77-84 are dependent from cancelled base claims. Hence, it is not clear what the metes and bounds are in reference to in view of the scope of the invention. The metes and bounds cannot be adequately determined based on cancelled claims 1, 10, 15 from which claims 63-75 and 77-84 are dependent. Furthermore, it is unclear as to which claim as disclosed is claimed to be the most comprehensive or the most limiting. The instant claim set does not distinctly claim the subject matter commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 62-85 (for compact prosecution, claims 63- 75 and 77-84 are treated dependent from claim 62) are rejected under 35 U.S.C. 103(a) as being unpatentable over Crenshaw et al. (USPN 5,151, 448), Krushinski et al. (USPN 5, 576,321) in view of Smith et al. (USPN 6,037,360) and Grass et al. (USPN 6,542,858 B1) and Bick (USPN 4,940,731) in view of Hirai et al. (USPN (4,659,696), Uda et al. (USPN 4,670,419), and Rubsamen et al. (USPGPUB 2004/0208829).

Crenshaw et al. teach premature ejaculation by a male human patient is treated by administration of fluoxetine (abstract only).

Crenshaw et al. teach fluoxetine [which] is a known antidepressant and is commercially available under the trade designation Prozac.RTM. as fluoxetine hydrochloride. This compound can be represented by the formula as disclosed and is also known by its chemical name as **(.+-.)-N-methyl-3-phenyl-3-[(.lambda., .lambda.,.lambda.-trifluoro-p-tolyl) -oxy]propylamine hydrochloride.** The molecular weight of fluoxetine hydrochloride is 345.79. It is a white to off-white crystalline solid and exhibits a solubility in water of about 14 milligrams per milliliter (column 1, lines 64-68; column 2, lines 10-15 and 20-68)

It has now been found that premature ejaculation in a male human patient suffering from such an affliction can be effectively ameliorated and treated by the administration to the patient of an effective dose of fluoxetine either in its free base form or its acid addition salt form. Fluoxetine is an amine, and, as is well known, amines readily form acid addition salts with inorganic acids as well as organic acids (column 2, lines 20-27).

The term "fluoxetine," as used herein and in the appended claims, means the free base form as well as an acid addition salt form of **(.+-.)-N-methyl-3-phenyl-3-[(.alpha.,.alpha.,.alpha.-trifluoro-p-tolyl)-ox y]propylamine.** (column 2, lines 28-30)

For the treatment contemplated by the present invention, the preferred route of administration is oral administration; however, **other routes of administration, e.g., parenteral, by suppositories, buccal dosage forms, skin patch, and the like**, can also be utilized. The active ingredient in the individual dosage forms can be **combined with the conventional pharmaceutical excipients and formed into tablets, capsules, and the like**. Tablets may be scored for divided dosage administration. Alternatively, the active ingredient

may be dissolved in a suitable liquid vehicle such as water, fruit juice, or the like. For chronic administration of the active ingredient oral dosage forms are preferred (column 2, lines 64-68; column 3, lines 1-8).

The dosage formulation drawn to suppositories is considered mucosal dosage forms in accordance with buccal dosage forms. The skin patch adequately teaches topical administration and "and the like" further supports and suggests variable forms of topical administration.

Crenshaw et al. teach the antidepressant fluoxetine is administered in an amount of between 5 milligrams to about 80 milligrams per day (column 1, lines 55 and 56).

Crenshaw et al. does not teach embodiments drawn specifically to serotonin, which is well-known intrinsic component inhibited by serotonin reuptake inhibitors such as fluoxetine.

However, Krushinski teach effective pharmaceuticals for the treatment of conditions related to or affected by the reuptake of serotonin and by the serotonin 1A receptor (abstract only).

Krushinski et al. teach [that] some of the present pharmaceuticals have a second activity as inhibitors of reuptake of serotonin. The best-known pharmaceutical with that efficacy is **fluoxetine** and the importance of its use in the treatment of depression and other conditions is extremely well documented and publicized. (column 1, lines 50-62).

Krushinski et al. does not teach fluoxetine in an inhalation dosage form.

However, Smith et al. teach the pharmaceutical compositions of the invention may also be administered by **nasal aerosol or inhalation**. Such compositions are prepared according to

techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, propellants such as fluorocarbons or nitrogen, and/or other conventional solubilizing or dispersing agents (abstract only).

Smith et al. teach the propensity to combine a serotonin reuptake inhibitor in concomitant therapy with a monoamine oxidase inhibitor. [However] like sertraline, paroxetine cannot be given to patients undergoing treatment with a **monoamine oxidase inhibitor**. Thus, the inventive objective of obviousness to try is adequately elucidated by the embodiment drawn to the subject matter of combining a (SSRI) and an (MAOI). In other words, based on similar classifications and mechanisms of action, the skilled artisan would have at once recognized characterization optimization with bioactive agents of the same general class (column 2, lines 21 and 22).

All the references mentioned above do not define, describe, or explain subject matter drawn to methods and protocols drawn specifically to pharmacokinetic modeling of variable dosage forms administered in concomitance.

Smith et al. teach a kit [which] is provided to assist an individual in administering a drug to treat premature ejaculation. Generally, the kit will include the following components: a pharmaceutical formulation comprising an active agent as provided herein; a device for effecting delivery of the pharmaceutical formulation; a container housing the pharmaceutical formulation during storage and prior to use; and instructions for carrying out drug administration in a manner effective to delay the onset of ejaculation (column 3, lines 45 and 46).

However, Grass et al. teach a pharmacokinetic-based design and selection tool (PK tool) and methods for predicting absorption of an administered compound of interest. [...].The PK tool and methods of the invention also finds use in selecting, designing, and preparing drug compounds, and multi-compound drugs and drug formulations (i.e., drug delivery system) for preparation of medicaments for use in treating mammalian disorders (abstract only).

Grass et al. essentially teach the well-known art of pharmacokinetic modeling in relation to multiple routes of administration (separately and in combination) and the varying rates of therapeutic efficacy thereof. Pharmacodynamics refers to the study of fundamental or molecular interactions between drug and body constituents, which through a subsequent series of events results in a pharmacological response. For most drugs the magnitude of a pharmacological effect depends on **time-dependent concentration of drug at the site of action (e.g., target receptor-ligand/drug interaction). Factors that influence rates of delivery and disappearance of drug to or from the site of action over time include absorption, distribution, metabolism, and elimination. The study of factors that influence how drug concentration varies with time is the subject of pharmacokinetics** (column 1, lines 18-29).

Grass et al. teach selected routes of administration include enteral (e.g., buccal or sublingual, oral (PO), rectal (PR)), parenteral (e.g., intravascular, intravenous bolus, intravenous infusion, intramuscular, subcutaneous injection), inhalation, and transdermal (percutaneous) (column 14, lines 20-25).

Thus, Grass et al. teach embodiments replete with teachings directed to the state of the art. Grass et al. discloses well-known parameters. The reasoning drawn to the mechanics of drug-

agent administration and concomitant therapy with several distinct dosage forms to treat the same disease state are contained in the following:

The physiological models are selected from a repository of **delivery route-specific models** stored in a memory, a database, or created de novo. Physiological models of the invention include those corresponding to **common routes of administration or barriers to absorption, such as oral (GI tract), ocular (eye), transdermal (skin), rectal, intravenous, rectal, subcutaneous, respiratory (nasal, lung) blood brain barrier and the like.** For constructing a model de novo, the basic approach is to identify and isolate a primary barrier to a specific absorption event from secondary events so that each barrier to absorption can be tested and validated in isolation. This involves selecting a site of administration that is separated from a sampling site by a primary physiological barrier to absorption and then building a developmental physiological model that incorporates rate process relations and limitations to describe the isolated absorption event. **If desired, the secondary events can be added sequentially so that each additional layer of complexity to the model can be tested and validated in isolation from other components of the initial model** (column 15, lines 48-67).

The simulation model is a mathematical model of a multi-compartment physiological model of a mammalian system (e.g., GI tract) that corresponds to the selected route of administration (e.g., oral). A given physiological model is represented by series of differential equations that **describe rate process interactions among anatomical segments for the physiological system under investigation.** The individual segments or compartments are represented mathematically as a one, two and/or three compartment kinetic system. The segments are linked in a stepwise fashion so as to form an integrated physiological model

describing absorption of a compound relative to the anatomical segments and at least one sampling site for assessing an absorption event in isolation. For a model simulating oral delivery, anatomical segments of the GI tract are provided, which can include the stomach, duodenum, jejunum, ileum and colon. A sampling site for the GI tract may be the portal vein and/or plasma. **The rectum and colon would be applicable for modeling a rectal route of delivery. Segments and sampling site for buccal or sublingual delivery routes can include the mouth, cheek/tongue tissue and plasma. For ocular routes, this can include aqueous humor, conjunctival sac, tear duct, nasal cavity and plasma. For the lung routes, this can include respiratory bronchioles zone and plasma. For delivery via the nose, this can include nasal cavity and plasma. For the topical and transdermal routes, this can include epidermal, dermal, subcutaneous tissue, muscle and plasma.** Other systems adhere to these basic designs (column 20, lines 6-34).

Thus, it would have been prima facie obvious to the one of skill at the time of invention to at once recognize a reasonable expectation of success via the incorporating and combining together all of the references above. Essentially, Crenshaw et al. teach the inventive objective of the claimed invention which is specifically drawn to premature ejaculation by a male human patient [who] is treated by administration of fluoxetine. Krushinski et al. provides the initial motivation to combine based on embodiments of explanations directed to the relation of the drug agents which are indicated for serotonin reuptake inhibition. The Smith et al. reference cures the deficiencies in the Crenshaw et al. and Krushinski et al. because it teaches serotonin reuptake inhibitor agent may be administered in an inhalation dosage form. Accordingly, the Crenshaw et al. teach mucosal and topical administration (column 2, lines 64-68; column 3, lines 1-8). Smith

et al. also teaches the embodiment drawn to the consideration of MAOIs in conjunction with SSRIs. Grass et al. encompasses the subject matter and inventive objective of the claimed invention by teaching pharmacokinetic modeling of the dosage forms as disclosed. Grass et al. teach the importance in consideration of the increased bioavailability of certain determined dosage forms in combination in order to treat the same disease state.

Claims 82-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crenshaw et al. (USPN 5,151, 448), Krushinski et al. (USPN 5, 576,321) in view of Smith et al. (USPN 6,037,360) and Grass et al. (USPN 6,542,858 B1) as applied to claim 65-81, 84, and 85 above, and further in view of and Hirai et al. (USPN (4,659,696).

Hirai et al. teach a pharmaceutical compositions for nasal or vaginal use (inhalation and mucosal).

Hirai et al. teaches a pharmaceutical composition which contains a hydrophilic drug, which is poorly absorbable through the gastrointestinal tract, and cyclodextrin and (2) a method of administering a pharmaceutical composition, which contains a hydrophilic drug, which is poorly absorbable through the gastrointestinal tract, and cyclodextrin from the nasal cavity, the vagina or rectum (abstract only).

Thus, Hirai et al. teach the well-known component of cyclodextrin in conjunction with bioactive agents as disclosed above.

Based on the references disclosed, there is an adequate amount of objective evidence present in the application to be made obvious over the references cited. The level of ordinary skill in the art would instantly recognize the necessity to optimize characterization of the composition used in the method of treating premature ejaculation. The differences in the

references cited above are not so different form the inventive objective of the claimed invention. The skilled artisan would instantly be inclined to recognize the therapeutic necessity of maximizing forms of administration to treat a specific disease state.

Further, applicants disclose several antidepressants in instant claim 77 and instant claim 80. However, these agents are generally within the same classification with similar mechanisms of action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617

TEB